NIEHS
National Institute of Environmental Health Sciences

# Genotype/Phenotype NIEHS Conference: Keynote "Building on a Genomic Infrastructure to Understand Environmentally Induced Human Disease

**December 05, 2005**

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Director
National Institute of Environmental Health Sciences

U.S. Department of Health and Human Services
National Institute of Health
National Institute of Environmental Health Services

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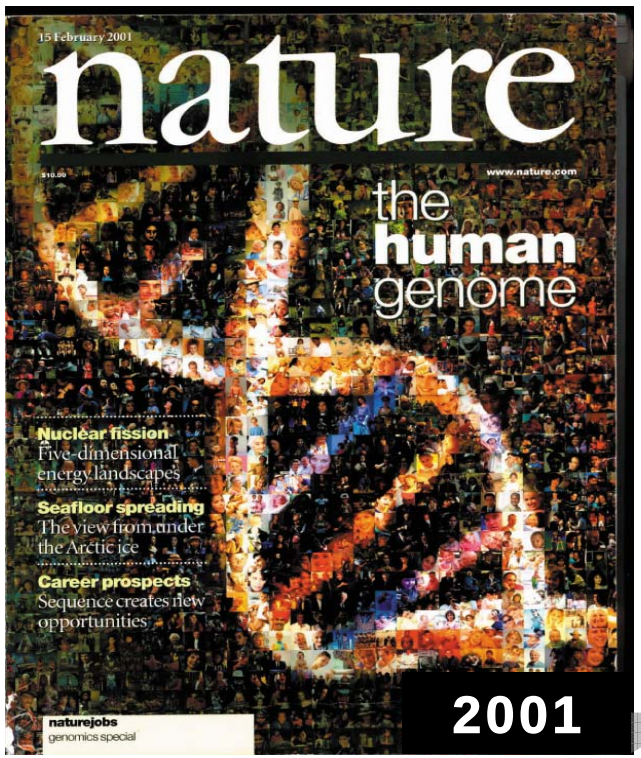
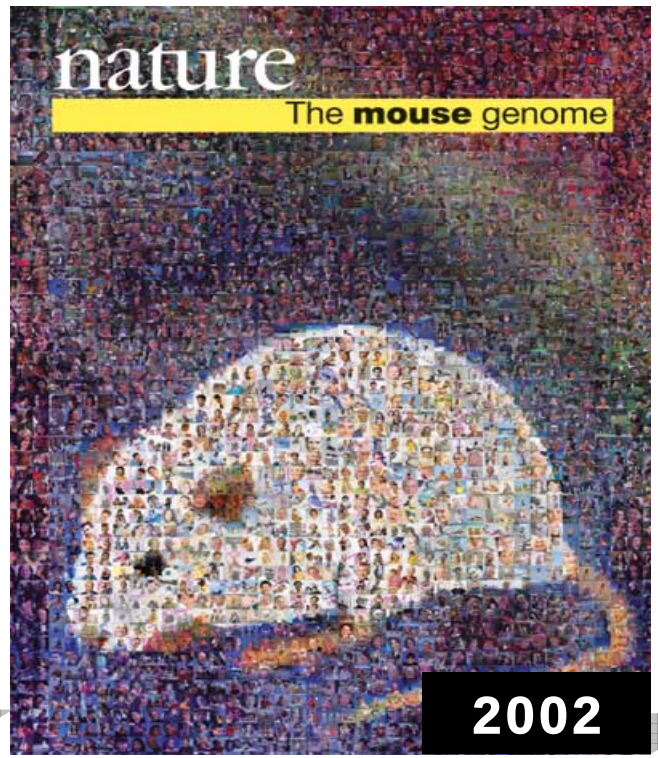
# Environmental Genetics and Genomics

- Scientific Opportunities
- Infrastructure Needs
- Priorities for Program Development

U.S. Department of Health and Human Services
National Institute of Health
National Institute of Environmental Health Services





***Genes are only a small part of our make-up…***
***the environment has a spectacular impact***

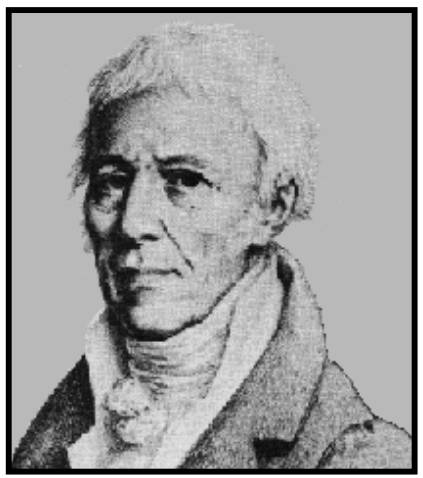
**Eric Lander**

# Environmental Genetics and Genomics

# Environmental Epigenetics

***Lamarckism Revisited***

**Inheritance *of* *Acquired Traits***



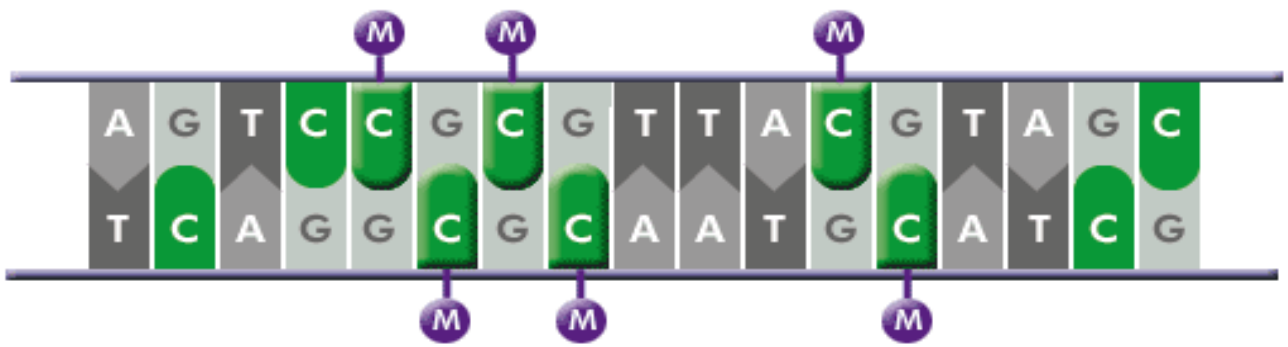
**1744-1829**

**Environmental Stress** → **Gene Expression** → **Inherited Adverse Health Outcome**

# Mechanisms of Epigenetic Inheritance

***Inheritance not dependent on DNA sequence***

- **DNA Methylation – silences gene by methylating the cytosine of a CpG motif**




**Feinberg. *Nature Reviews* 2004; 4:143**

# Mechanisms of Epigenetic Inheritance

***Inheritance not dependent on DNA sequence***

- **DNA Methylation – silences gene by methylating the cytosine of a CpG motif**
- **Genomic Imprinting – differential methylation results in preferential silencing of maternal or paternal allele**
- **Histone Modification – methylation, acetylation, or phosphorylation of histone can regulate transcription of genes**

**Feinberg. *Nature Reviews* 2004; 4:143**

# Proof of Concept: Agouti Mice

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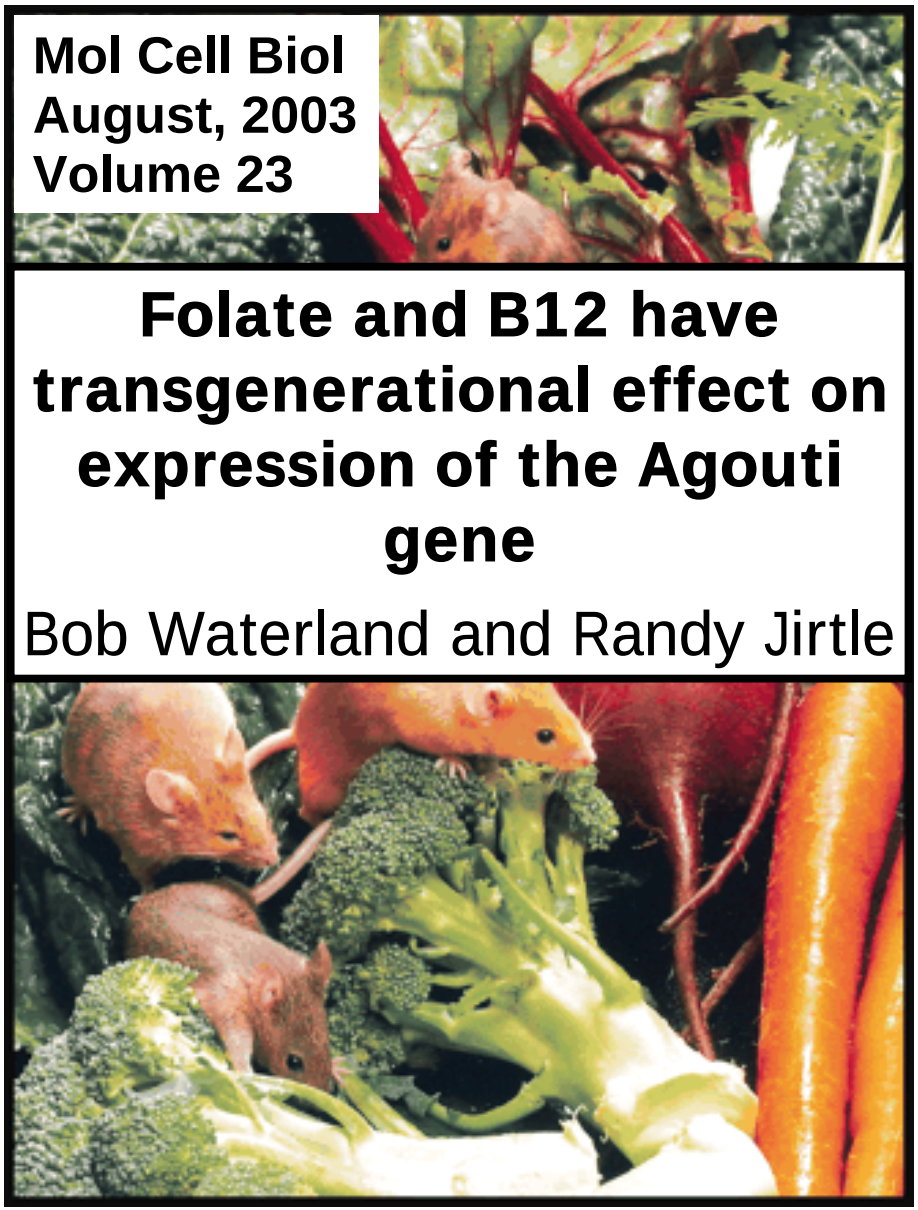
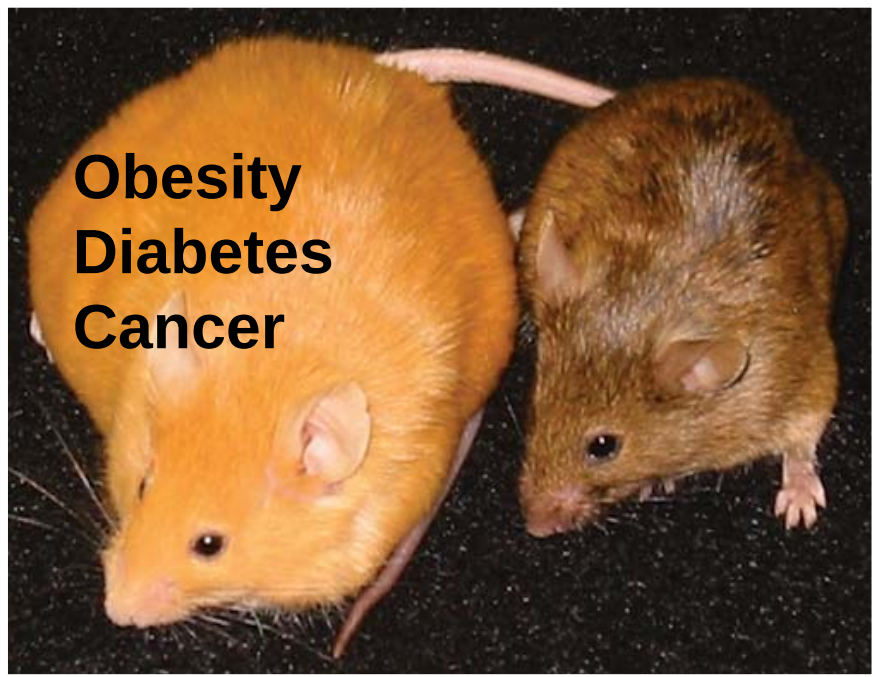
**Coat color in Agouti mice varies from black to yellow due to stochastic methylation of CpG motifs**

**Unmethylated *agouti* (expressed)**


**Methylated *agouti* (not expressed)**

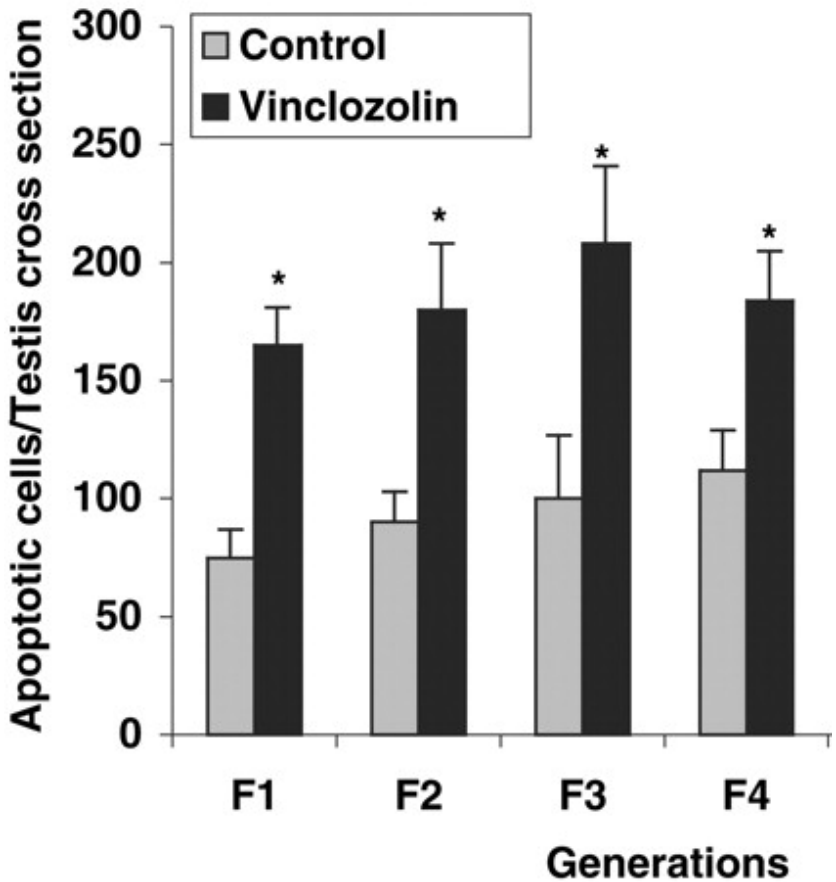



**Waterland. *Mol Cell Biol* 2003; 23:5293**

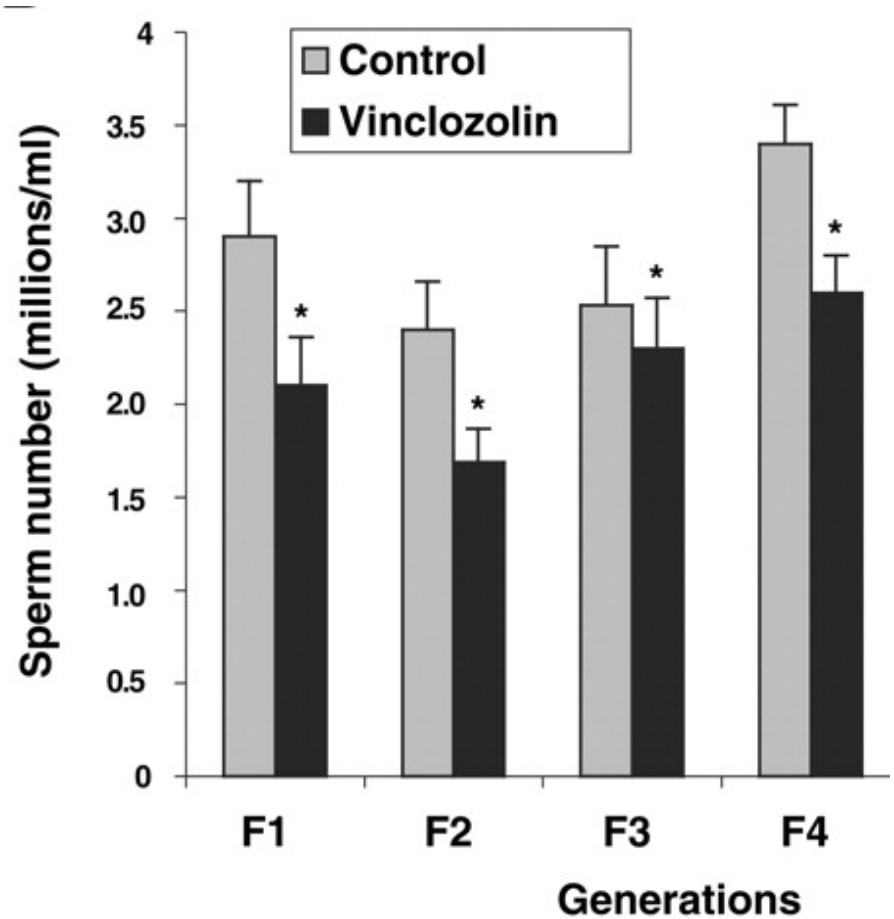

**Endocrine disruptors have transgenerational effect on male fertility**

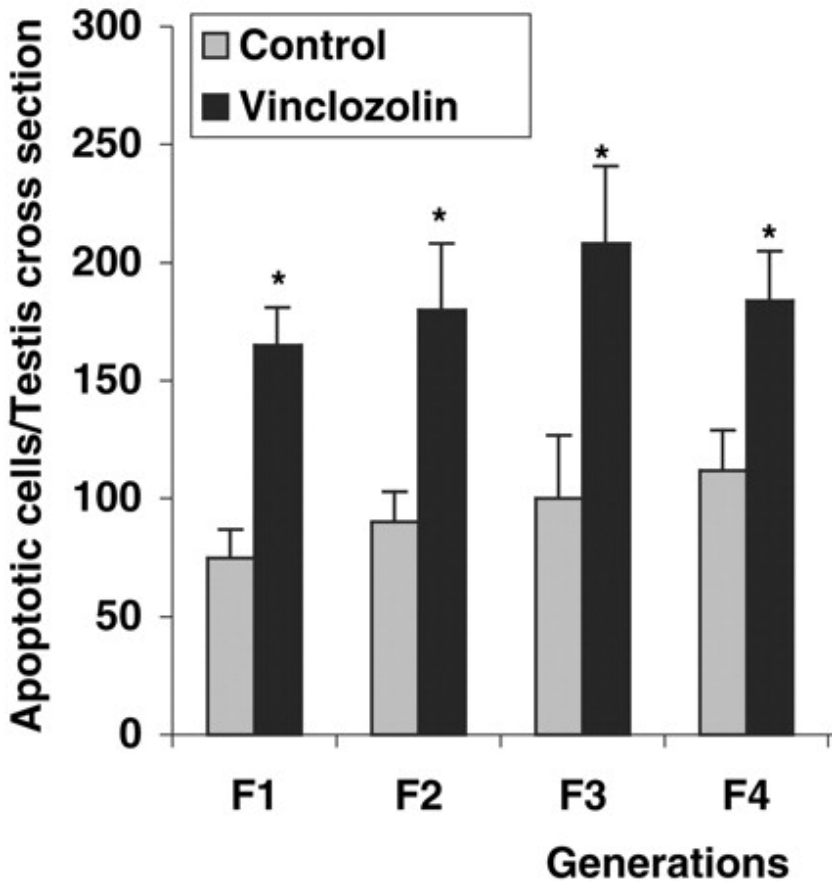
Matt Anway et al.




**Anway. *Science* 2005; 308:1466**

# Environmental Epigenetics

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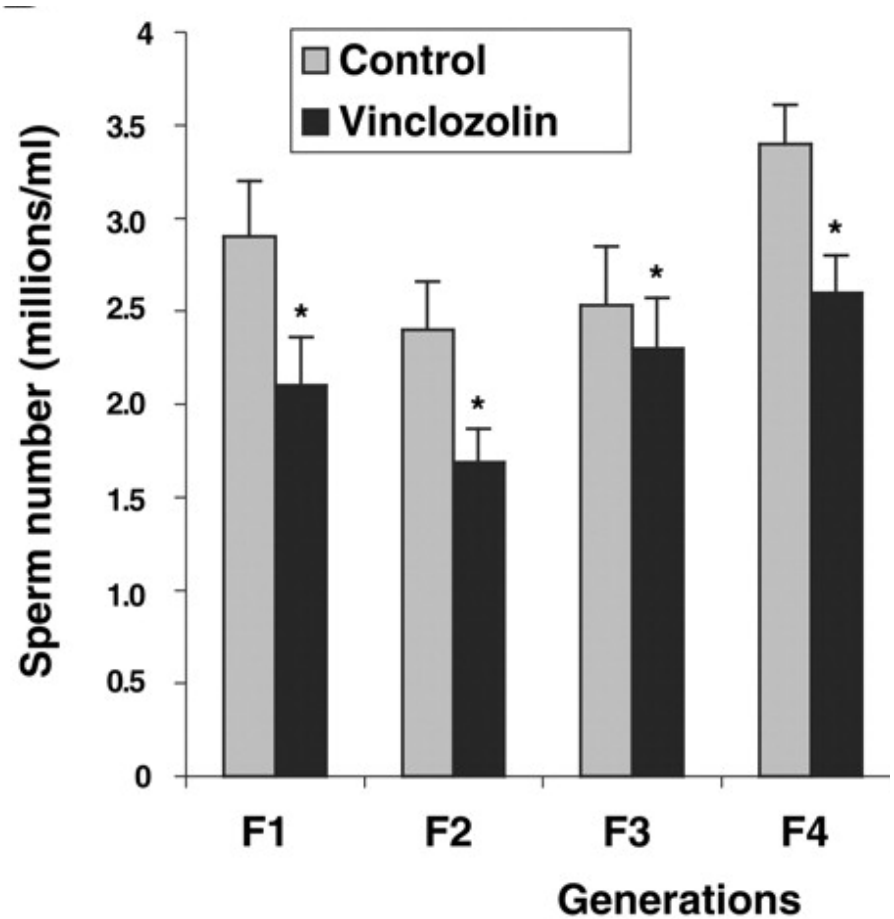
# Environmental Epigenetics



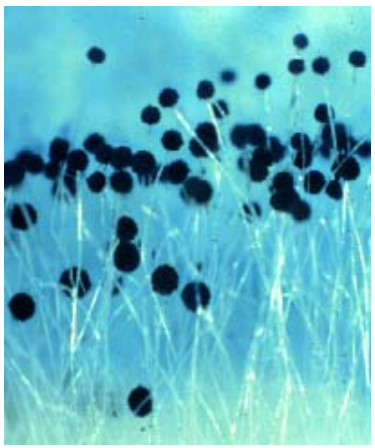

- **Effects of vinclozolin (antiandrogenic fungicide) on reproduction correlated with DNA methylation patterns of specific genes**
- **Effects transferred through male germ line**

**Anway. *Science* 2005; 308:1466**

# Environmental Genomics and Human Disease

# Environmental Genomics

***Beadle the first environmental geneticist (one gene – one enzyme)***

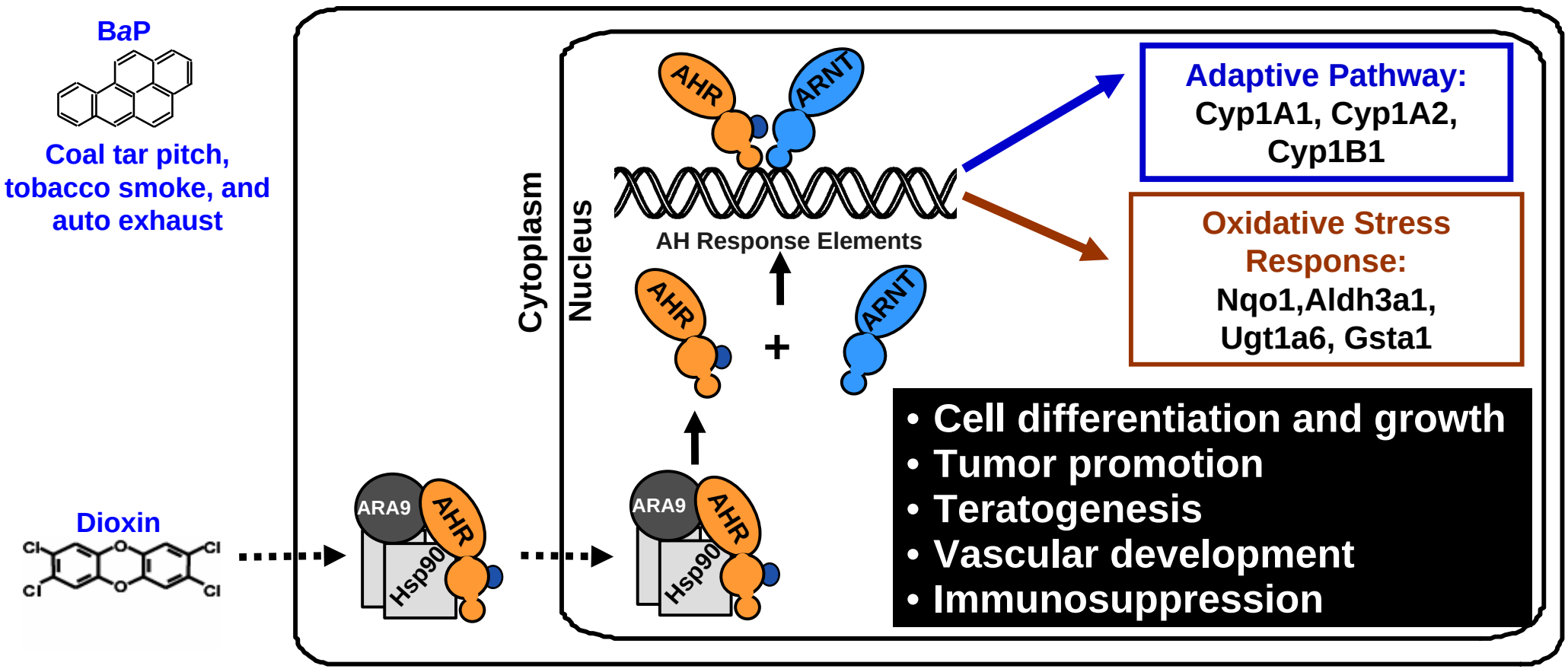


**1903-1989**

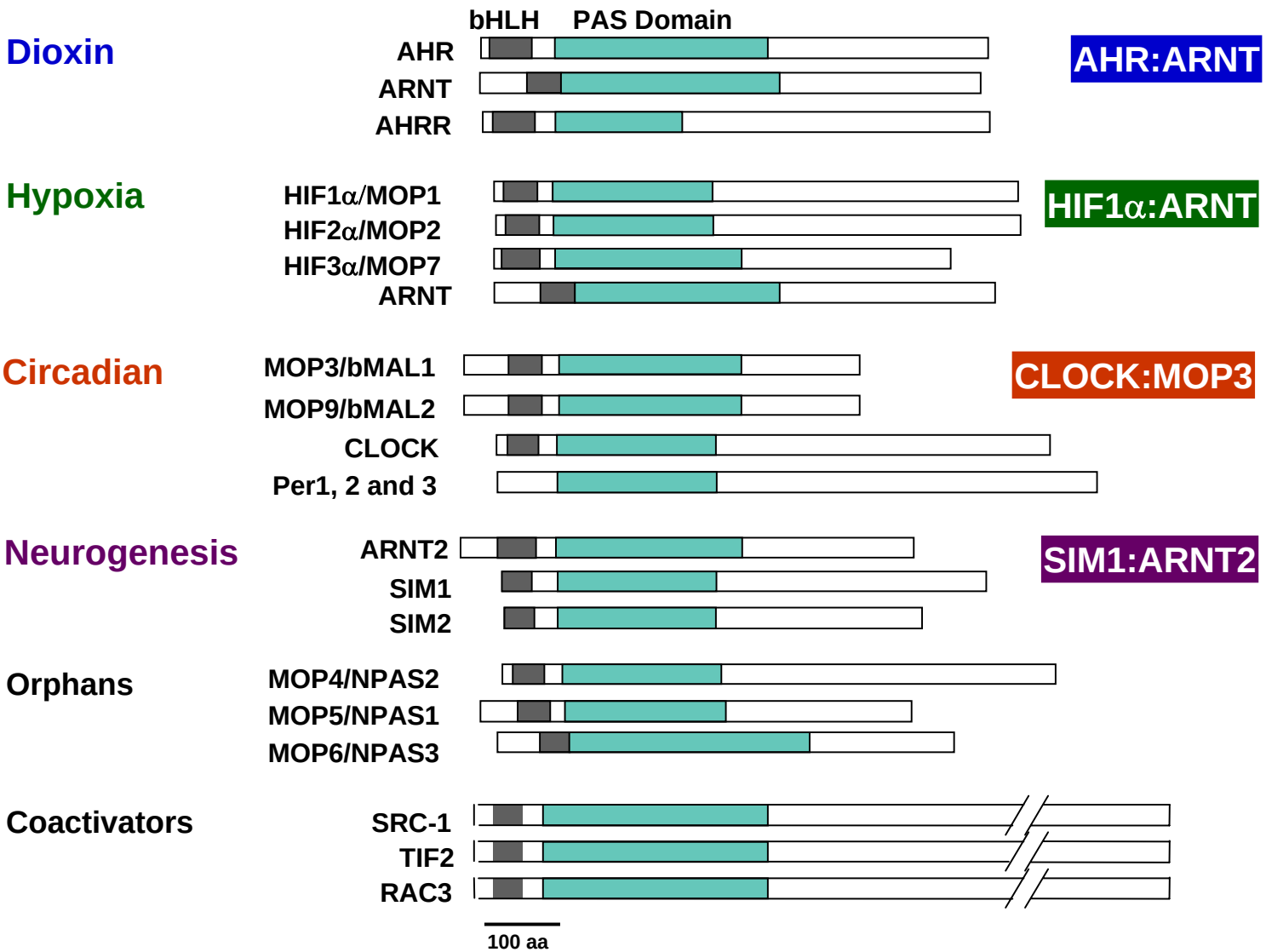
***Neurospora*** **(bread mold)** → **Radiation** → **Media to Select Mutants** → **Defective Gene** → **Defective Enzyme**

# Aryl Hydrocarbon Receptor (AHR)

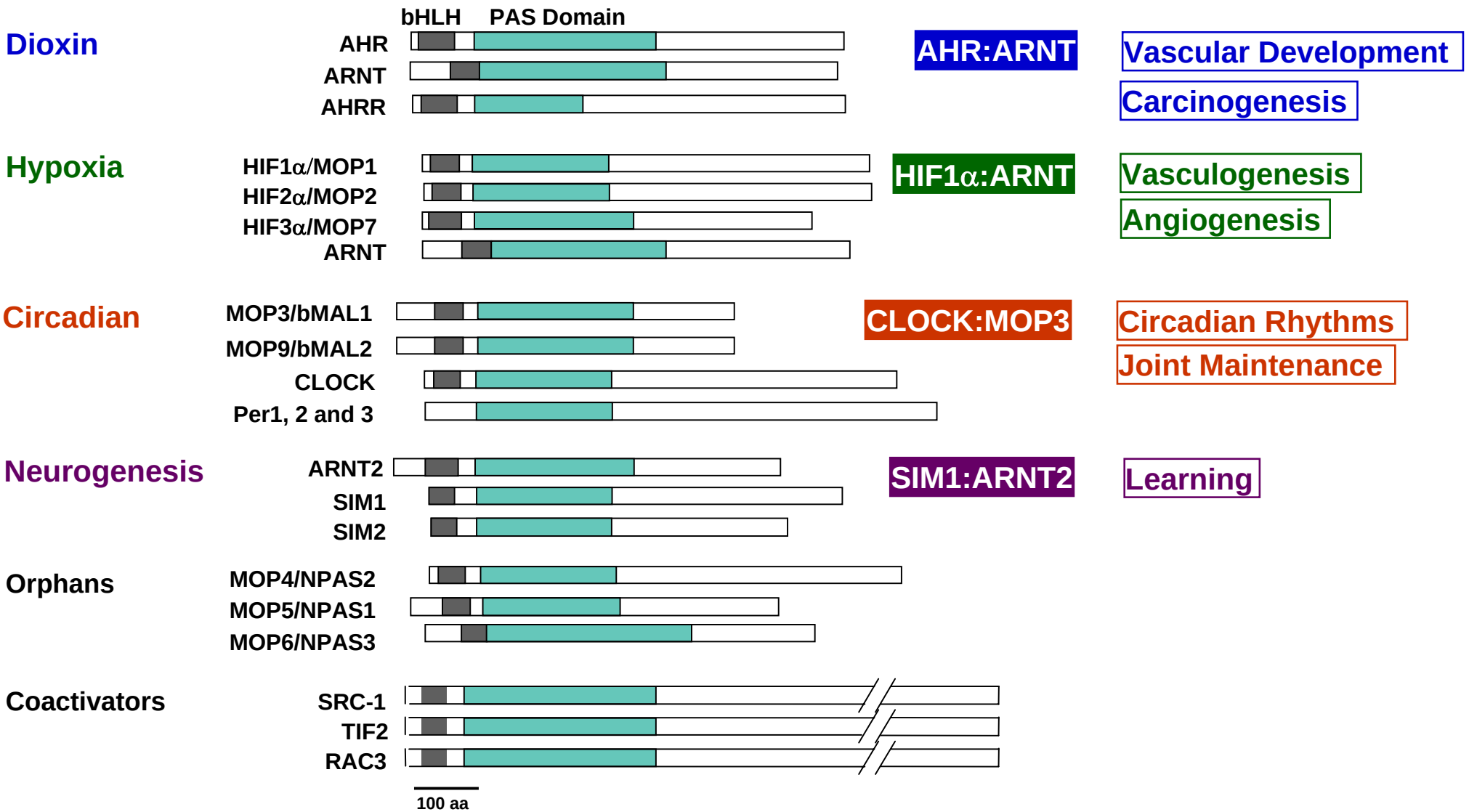
- Discovered due to the carcinogenicity of polyaromatic hydrocarbons
- One of the first receptors to mediate carcinogenesis (1st orphan receptor)
- Evolutionarily conserved (*C. elegans* to humans)



# PAS Superfamily: *Environmental Sensors*



# PAS Superfamily: *Physiologic Sensors*



# Exposures Can Simplify Complex Diseases

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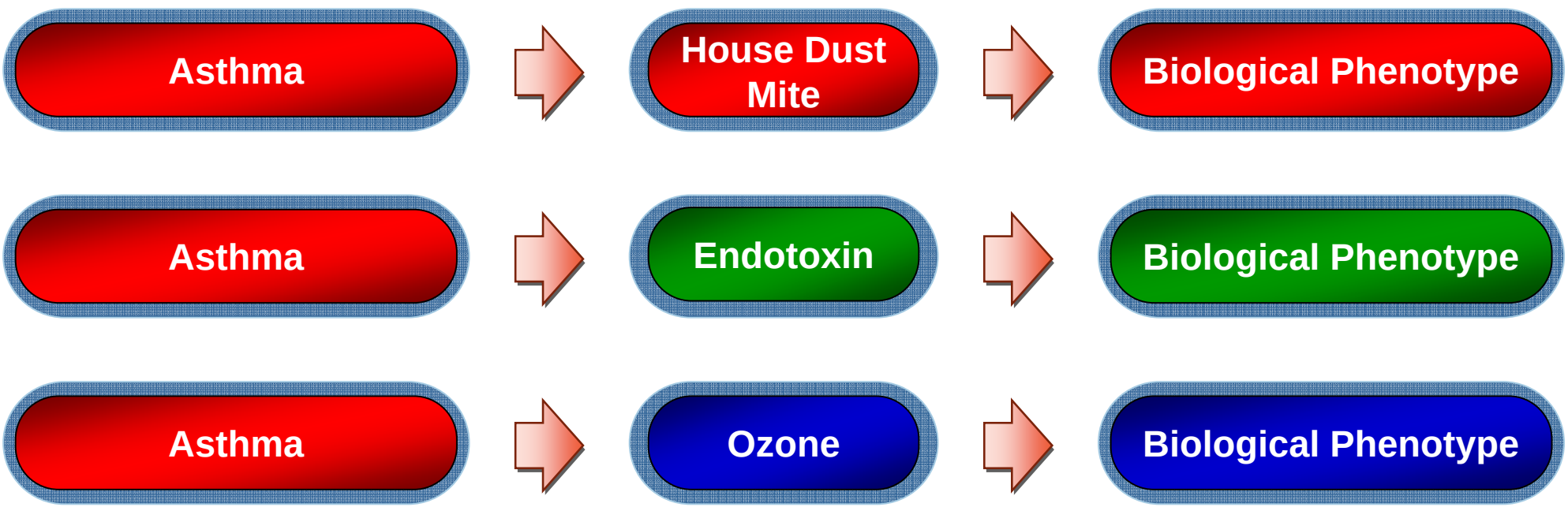

# Comparative Genomics

## *Evolutionary Conservation of Innate Immunity*

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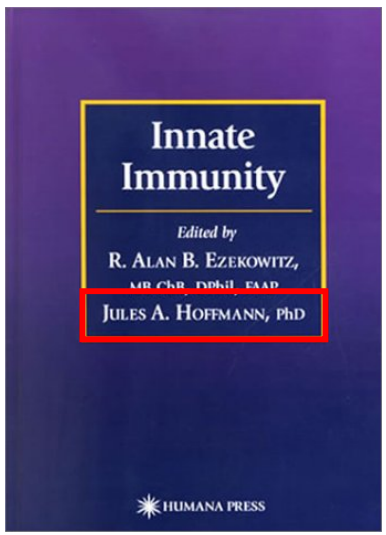
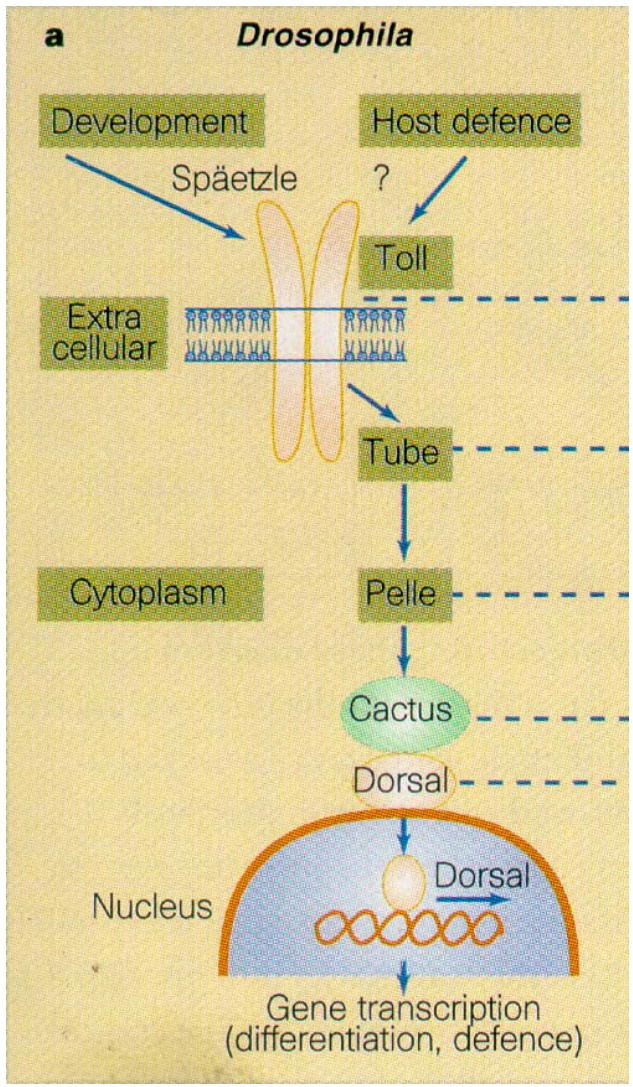
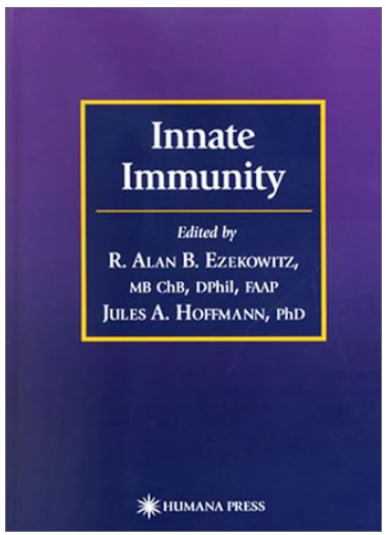
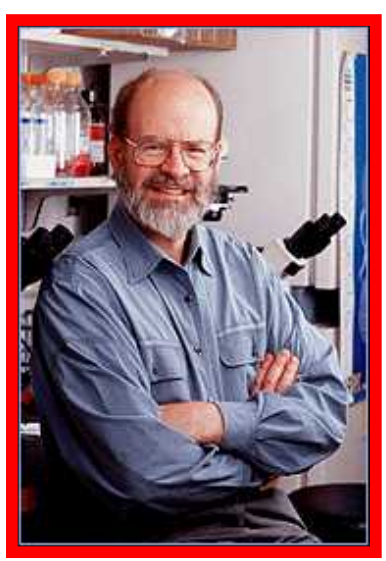


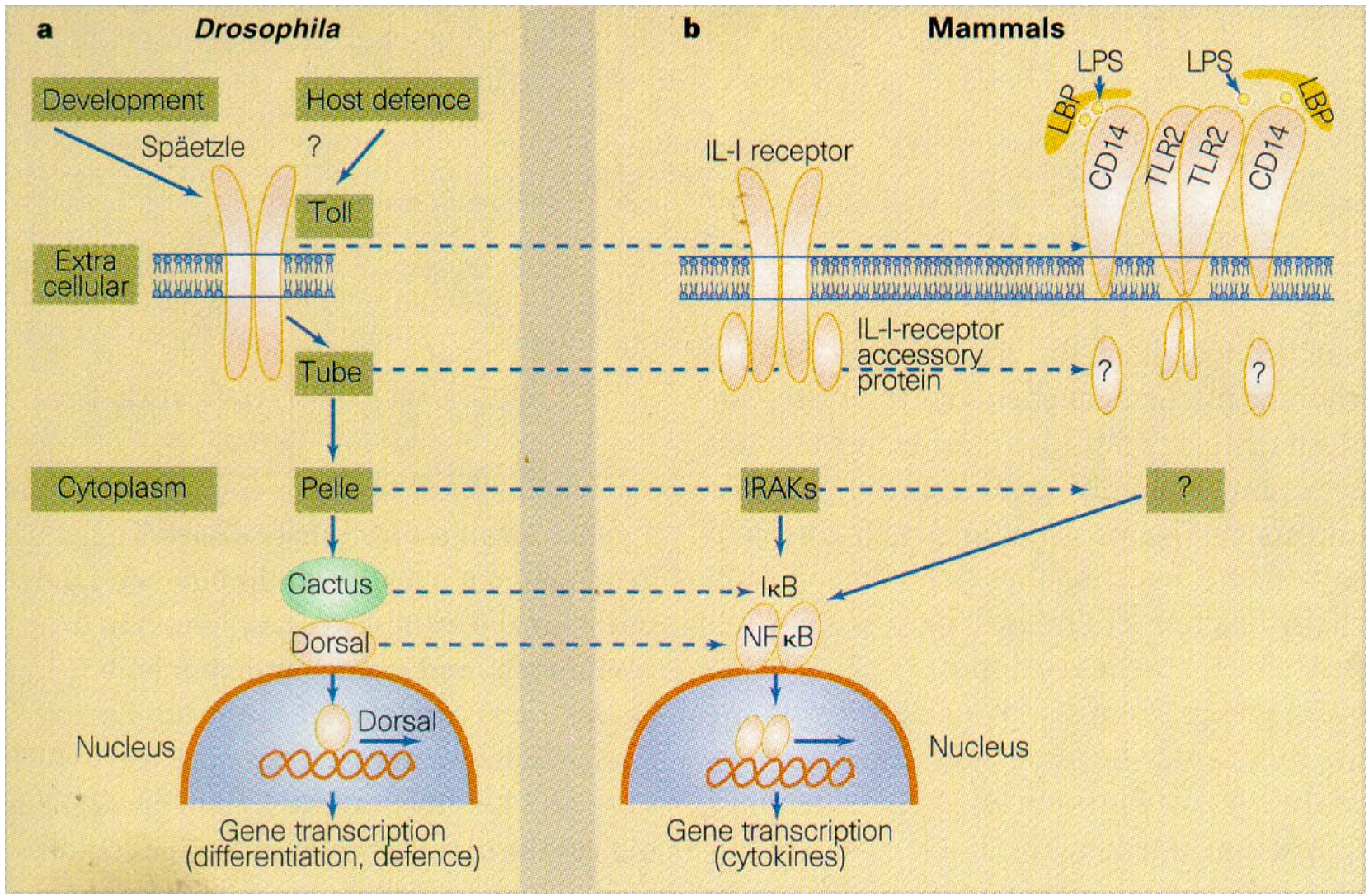



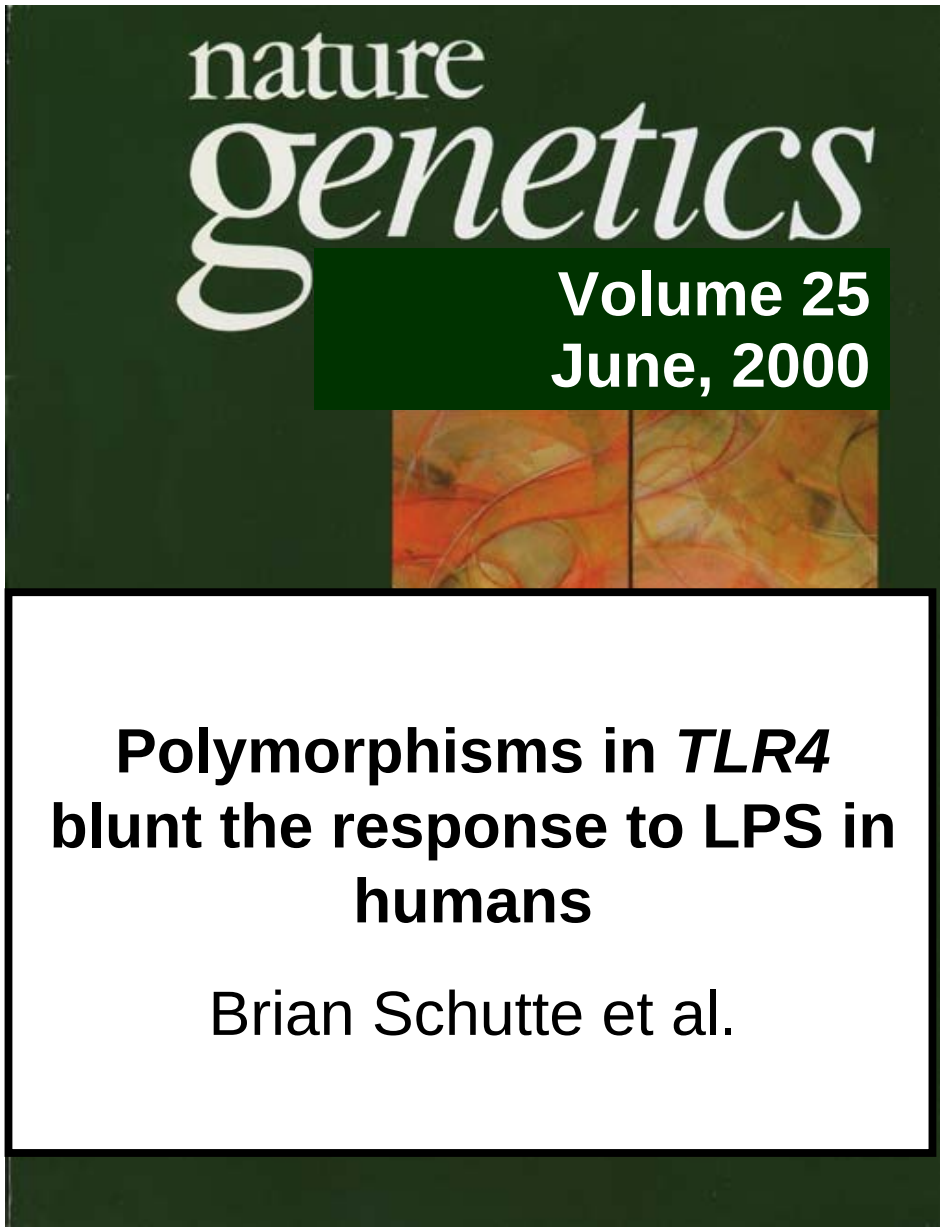

# Comparative Genomics

## *Evolutionary Conservation of Innate Immunity*



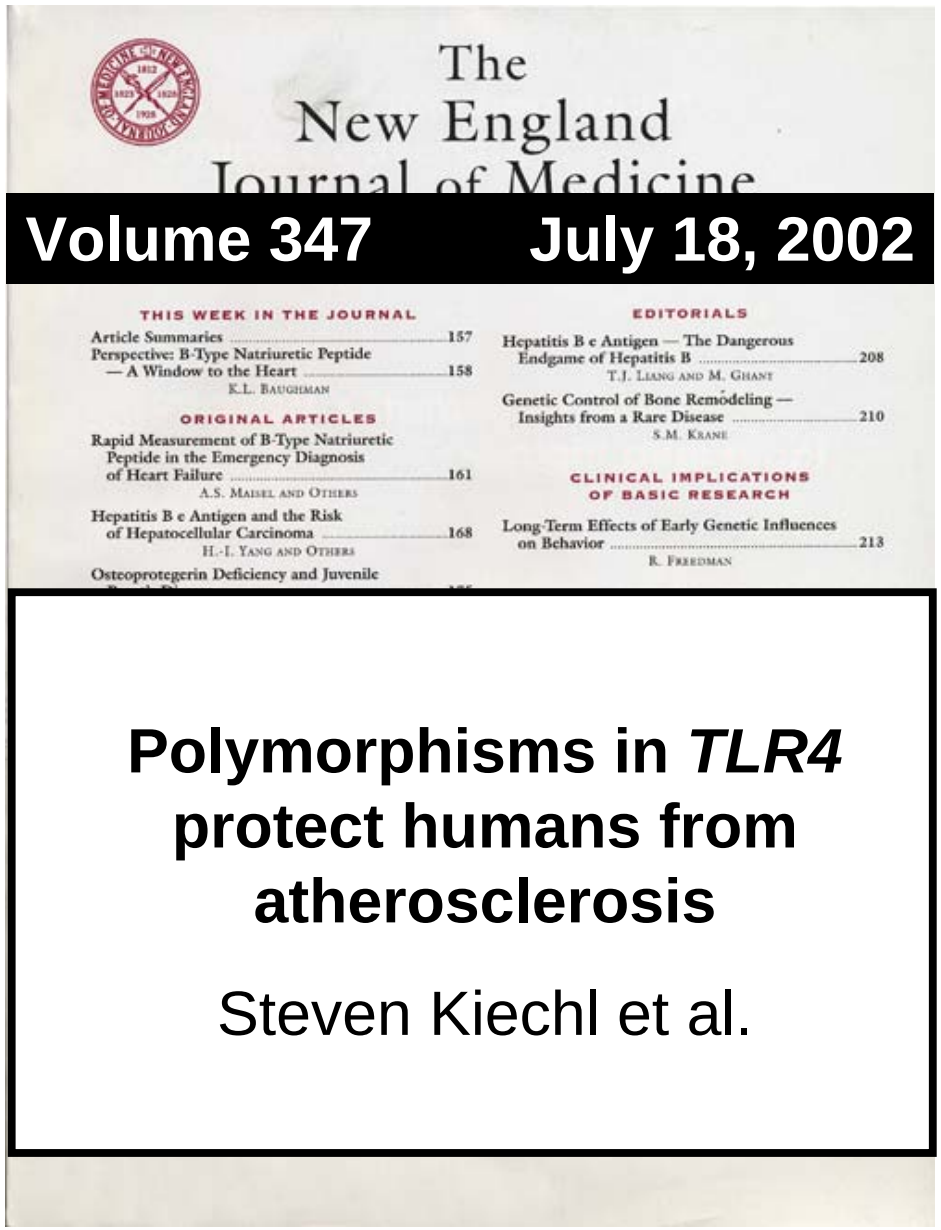








**Polymorphisms in *TLR4* blunt the response to LPS in humans**

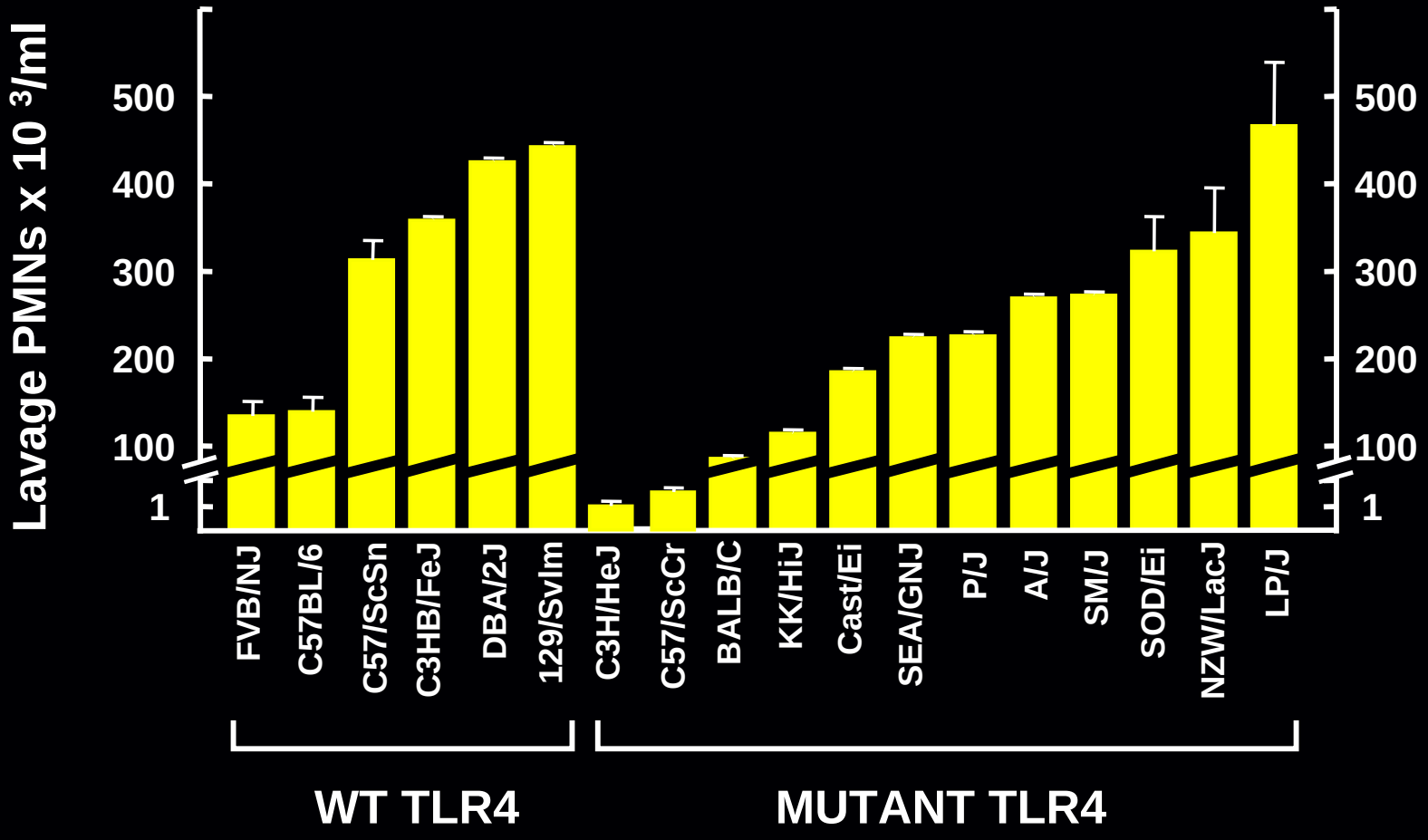
Brian Schutte et al.

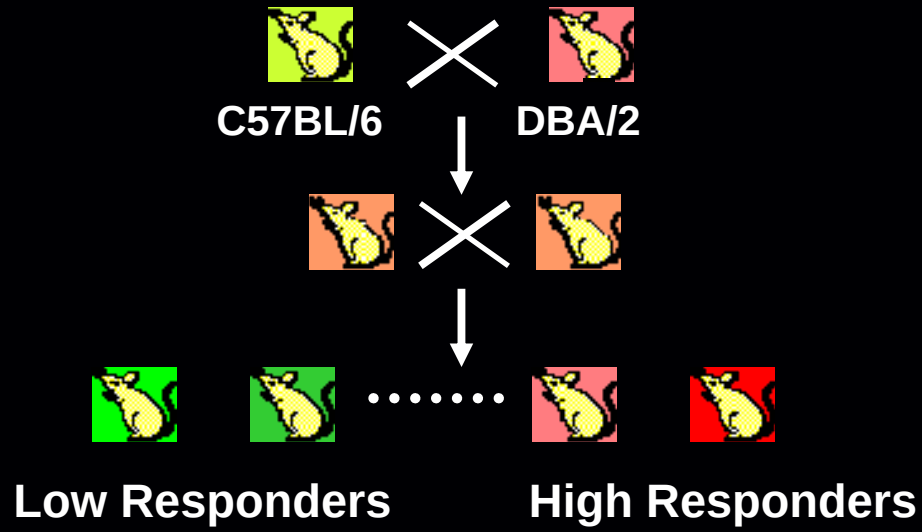


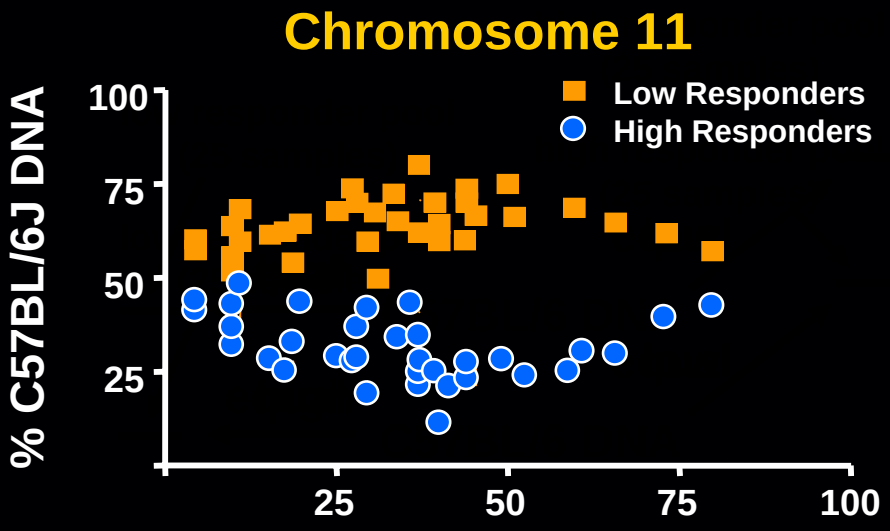

**Polymorphisms in *TLR4* protect humans from atherosclerosis**

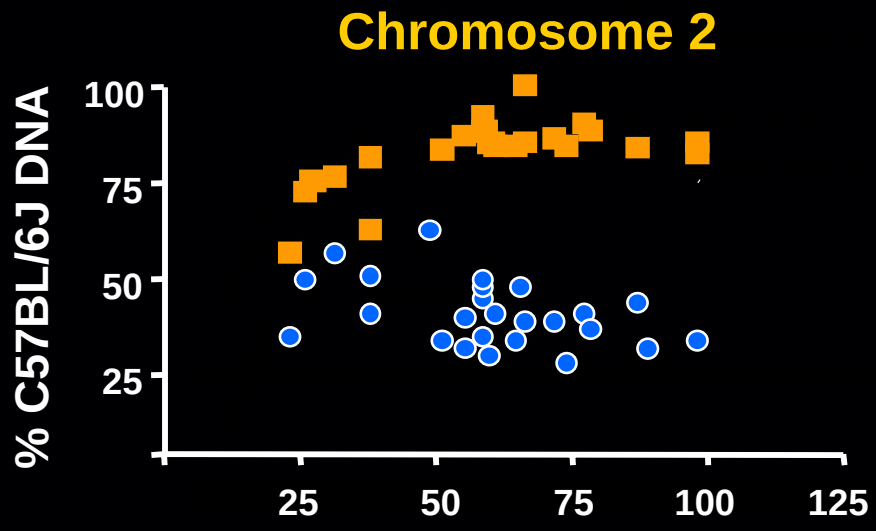
Steven Kiechl et al.

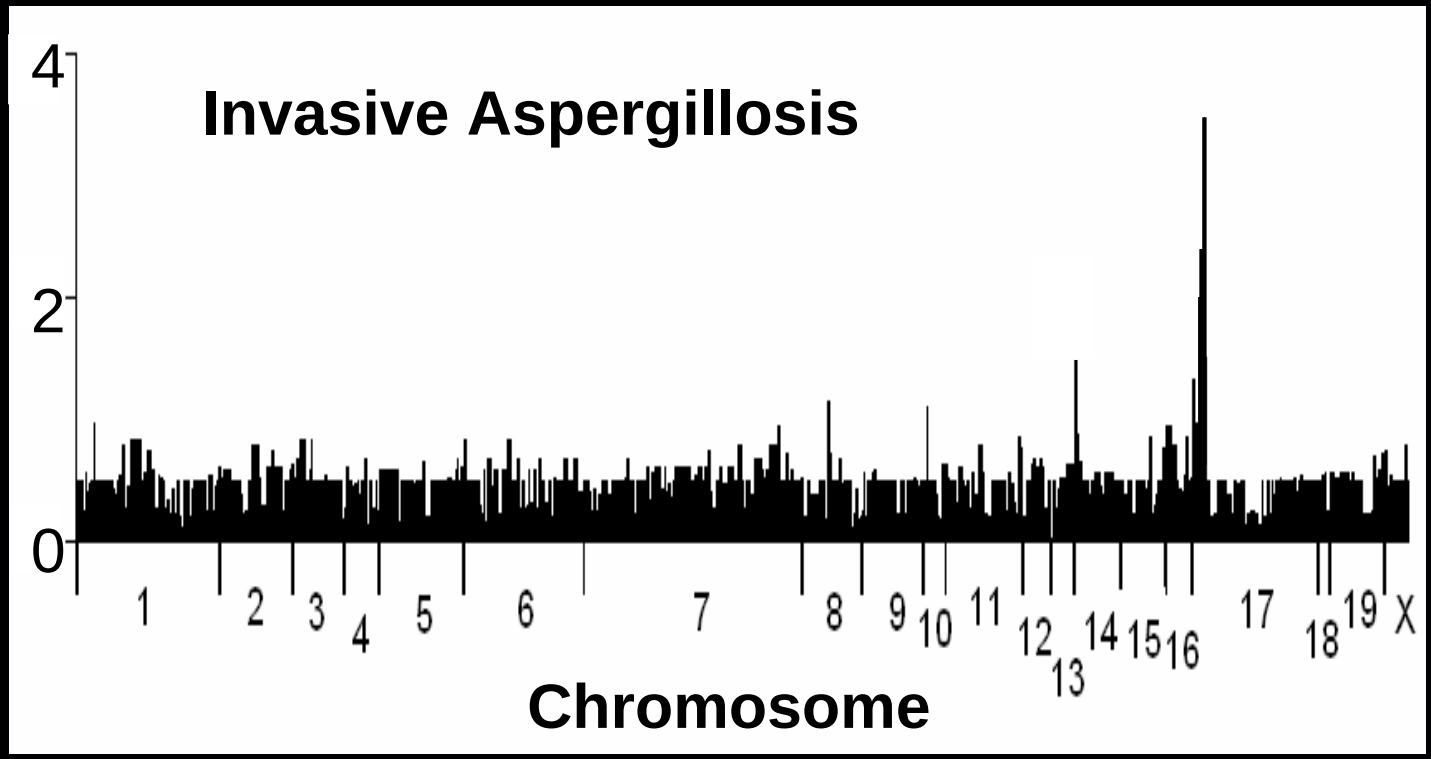
# LPS Responsiveness in Inbred Strains of Mice

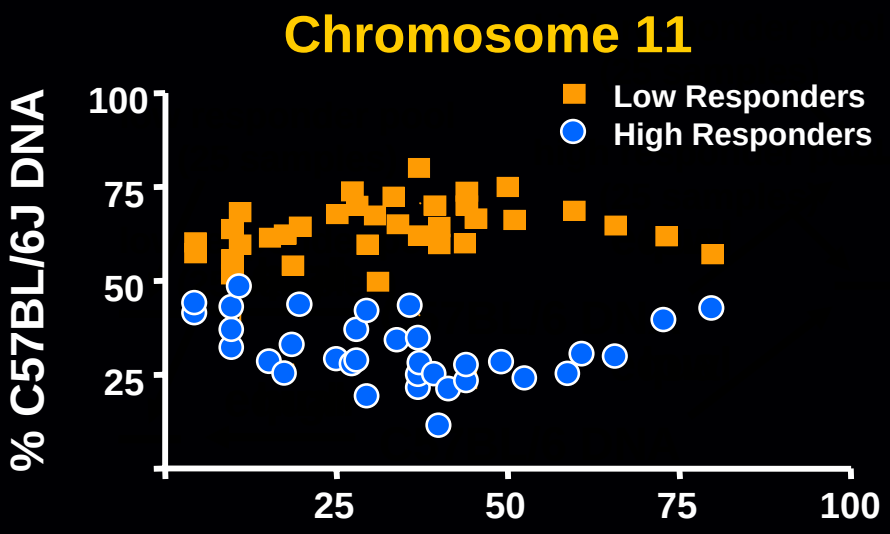


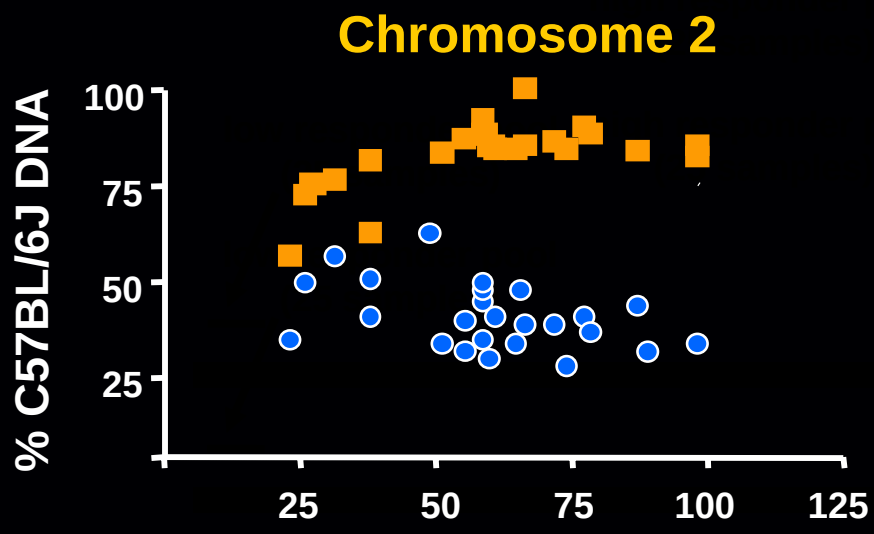

C57BL/6
DBA/2
Low Responders
High Responders


Chromosome 11
Low Responders
High Responders
% C57BL/6J DNA
100
75
50
25
25
50
75
100

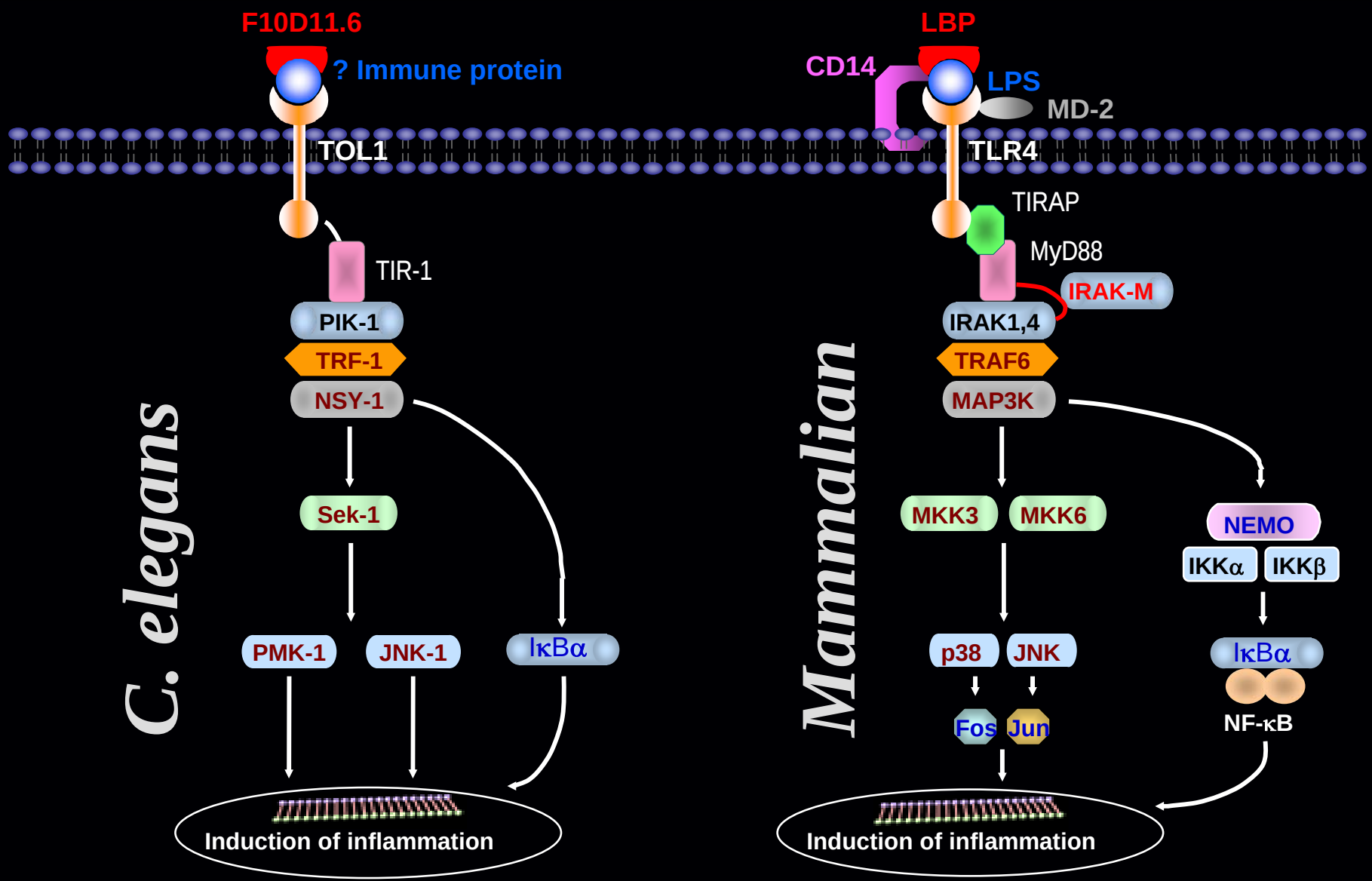

Chromosome 2
% C57BL/6J DNA
100
75
50
25
25
50
75
100
125


Invasive Aspergillosis
4
2
0
1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
X
Chromosome

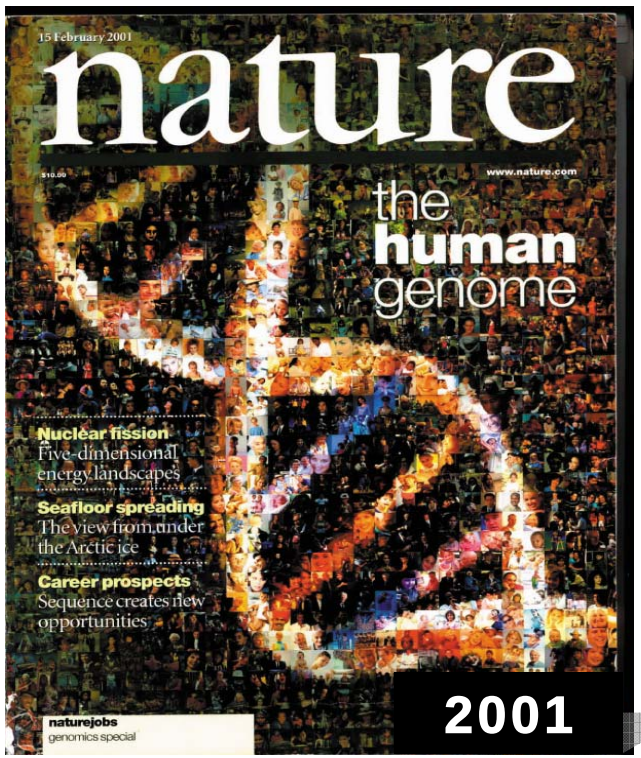

Chromosome 11
Low Responders
High Responders
% C57BL/6J DNA
100
75
50
25
25
50
75
100

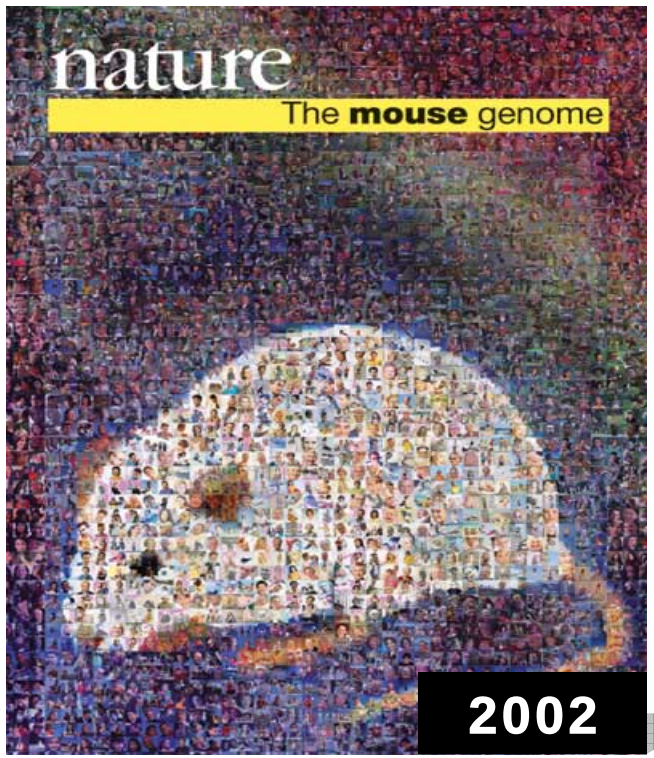

Chromosome 2
% C57BL/6J DNA
100
75
50
25
25
50
75
100
125

# Comparative Genomics in Innate Immunity



# Why Don't We Know More?



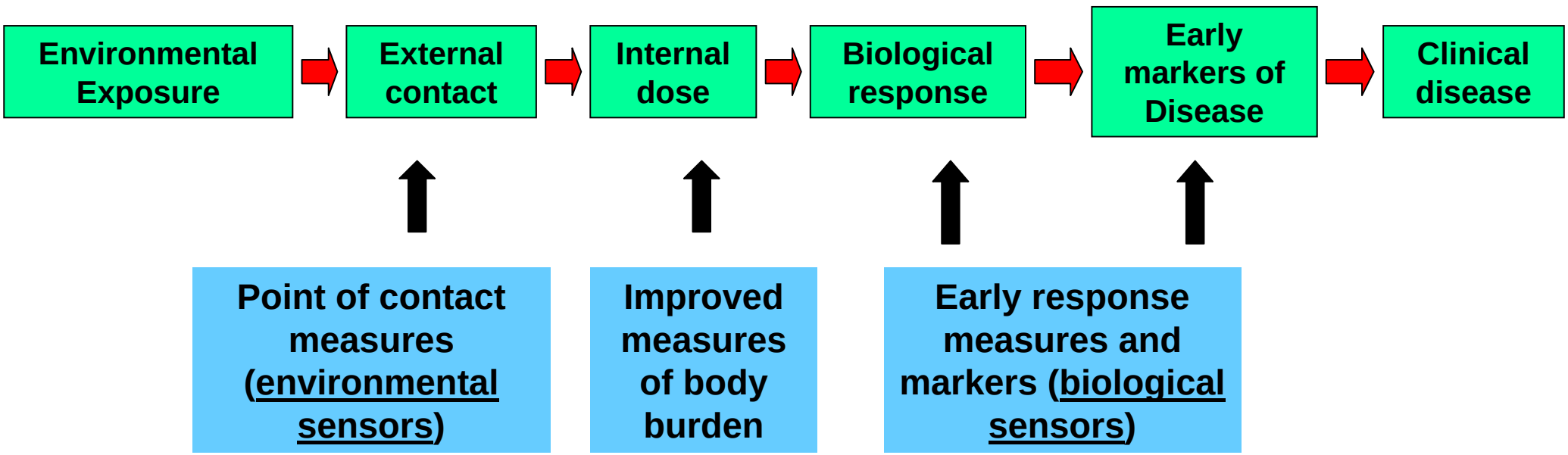





***Genes are only a small part of our make-up…***
***the environment has a spectacular impact***

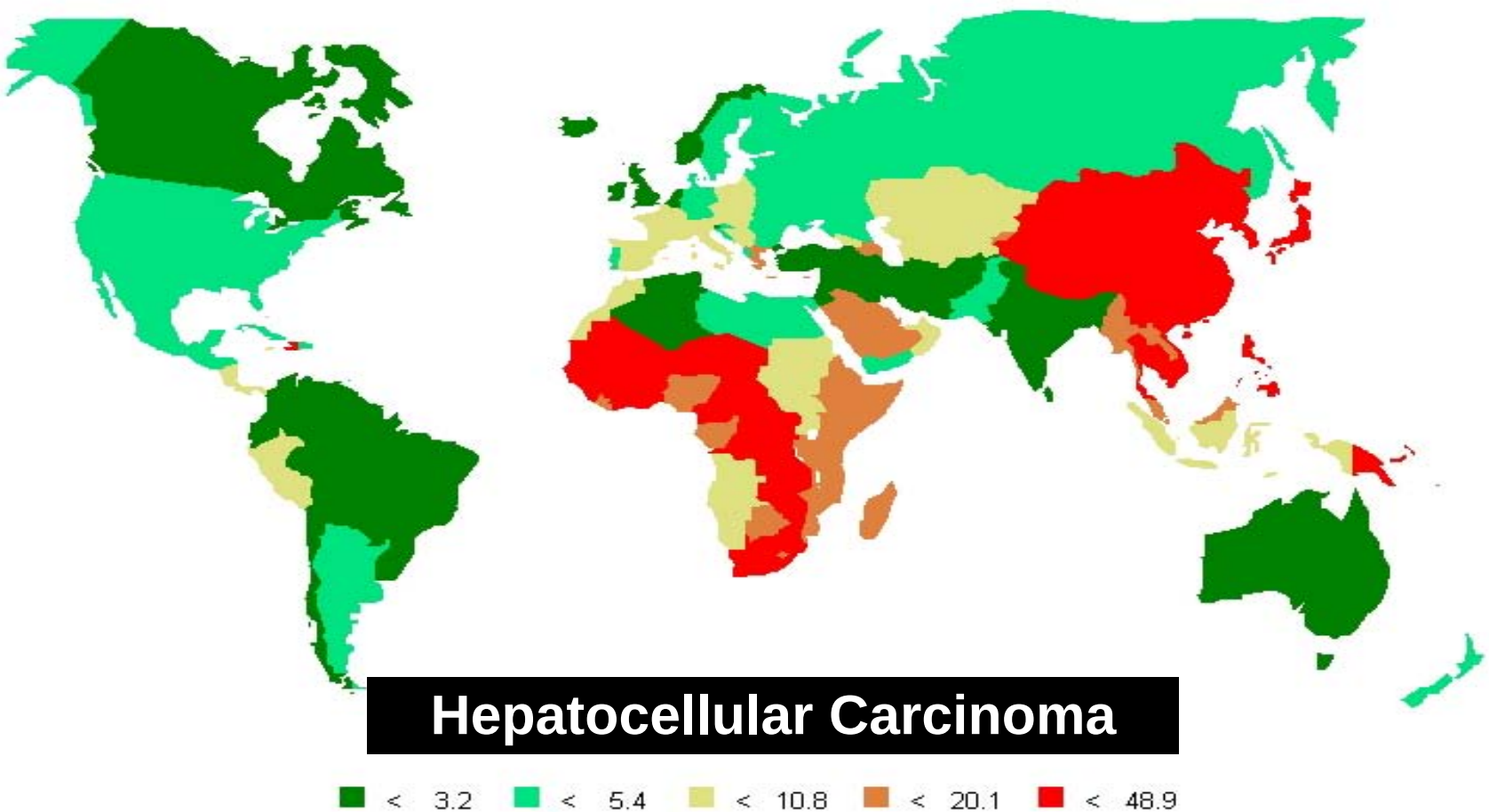
**Eric Lander**

# Infrastructure Needs: More Precise Markers of Exposure

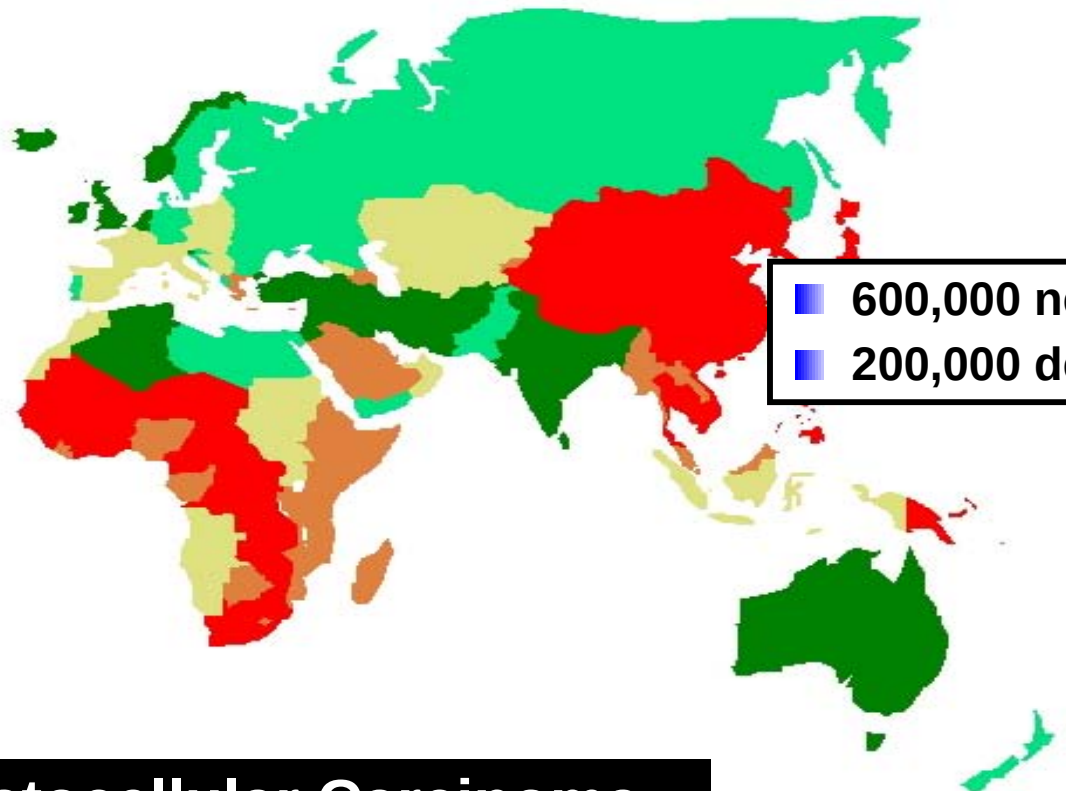



**Links personal exposures to biological response**

# Aflatoxin and Liver Cancer



# Aflatoxin and Liver Cancer

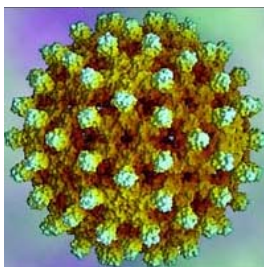


- 600,000 new cases
- 200,000 deaths

**Hepatocellular Carcinoma**

< 3.2 < 5.4 < 10.8 < 20.1 < 48.9

# Aflatoxin and Liver Cancer: Biomarkers

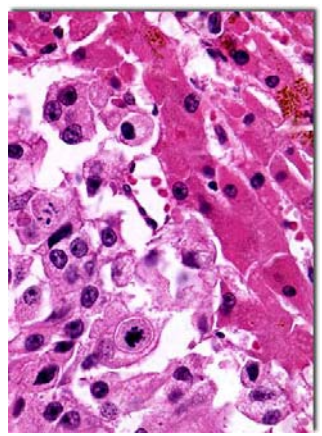


HBsAg (serum)

Insertional Mutagensis → Chronic Inflammation → Cell Proliferation

Reactive Intermediates → Promutagenic DNA Lesions → P53 Mutations

Hepatitis Cirrhosis

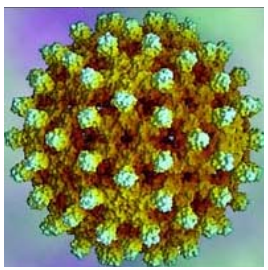


Aflatoxin Mercapturic Acid (urine)

Aflatoxin-N7-guanine (urine)

Arg249Ser Mutations (serum)

# Aflatoxin and Liver Cancer: Biomarkers



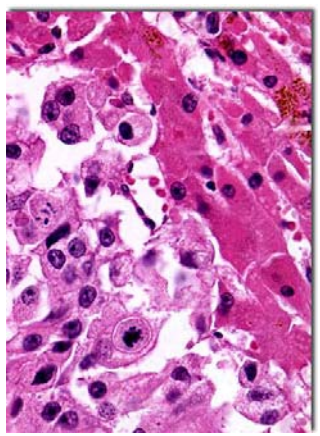
HBsAg (serum)

No association between dietary aflatoxin and liver cancer

Insertional Mutagensis → Chronic Inflammation → Cell Proliferation

Reactive Intermediates → Promutagenic DNA Lesions → P53 Mutations

Hepatitis Cirrhosis



Aflatoxin Mercapturic Acid (urine)

Aflatoxin-N7-guanine (urine)

Arg249Ser Mutations (serum)

| | RR |
|---|---|
| Aflatoxin | 3.8 |
| HBV | 7.3 |
| Aflatoxin + HBV | 60.0 |

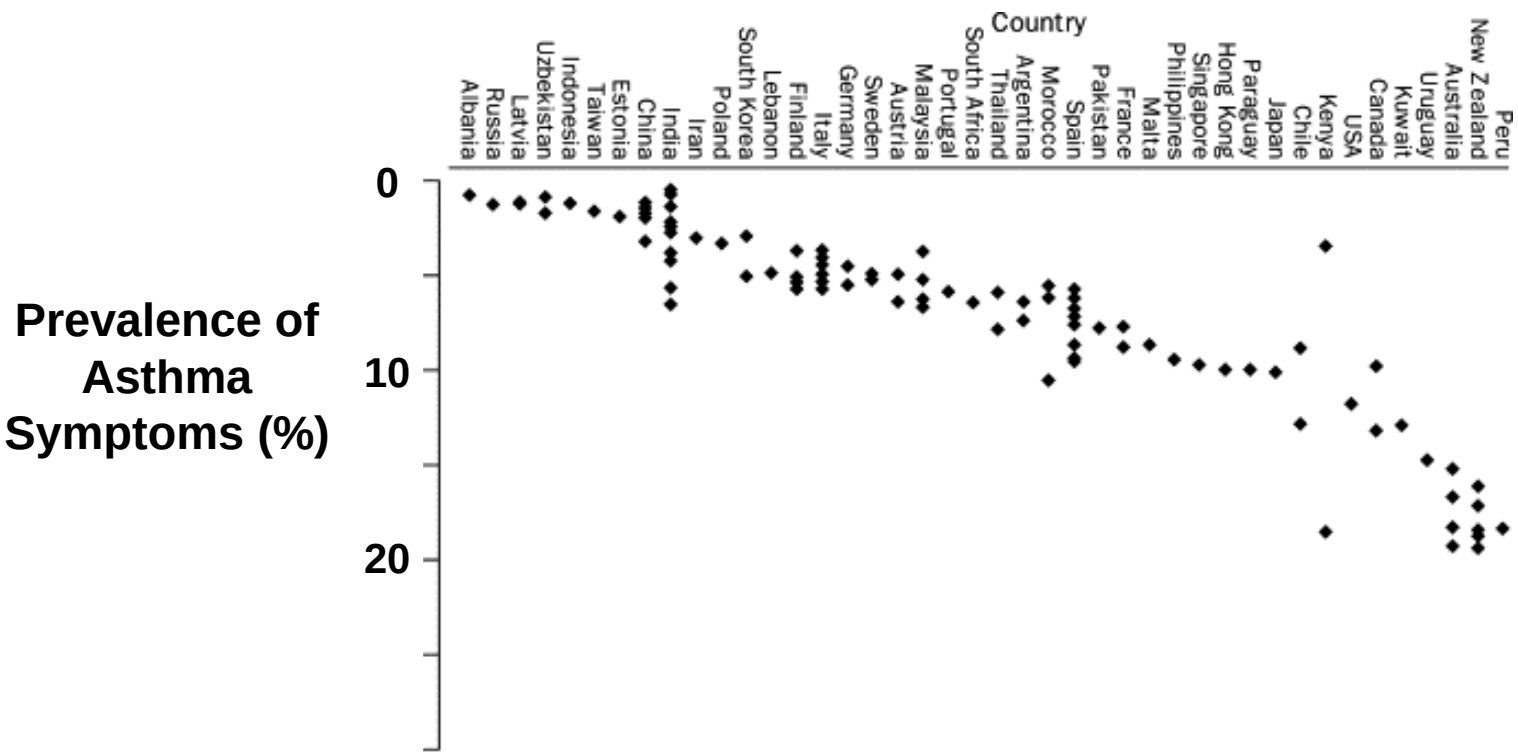
# Gene – Environment Prospective Cohort

- **Large sample size – at least 500,000**
- **Demographics and environmental exposures to match U.S. population**
- **Personalized exposure assessment**
- **Precise phenotypes**

**Effective approach to identify the role of genes and environment on the development of disease**

# Prioritize Diseases and Populations

- **International patterns of disease (rates, geographical distribution)**




**ISAAC. *Lancet* 1998; 351:1225**

# Prioritize Diseases and Populations

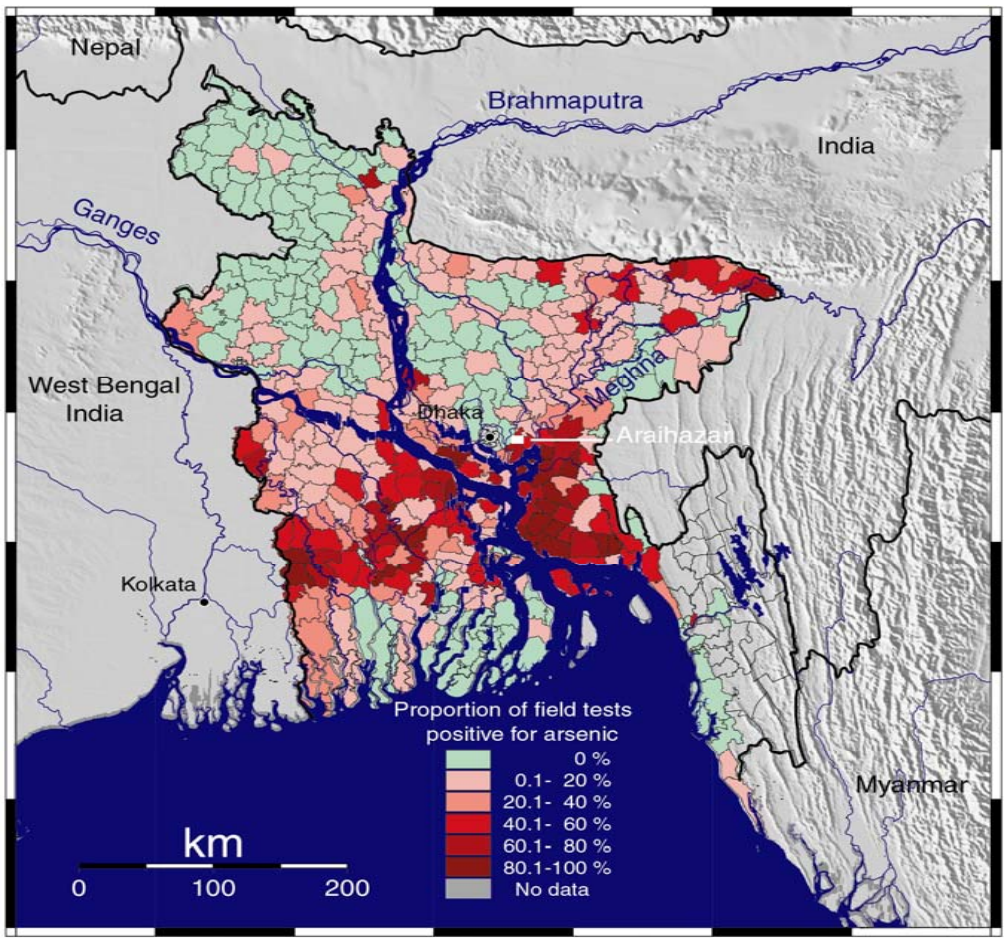
- **International patterns of disease (rates, geographical distribution)**
- **Familial and twin studies (genetic vs. environmental contribution to disease phenotype)**

| Population | MZ concord (%) | DZ concord (%) | Heritability (%) |
|---|---|---|---|
| Finland (adults) | 43 | 25 | 36 |
| Australia (adults) | 65 | 24 | 60-75 |
| Norway (18-25 yr) | 75 | 21 | 75 |
| Sweden (16 yr) | 76 | 45 | 79 |

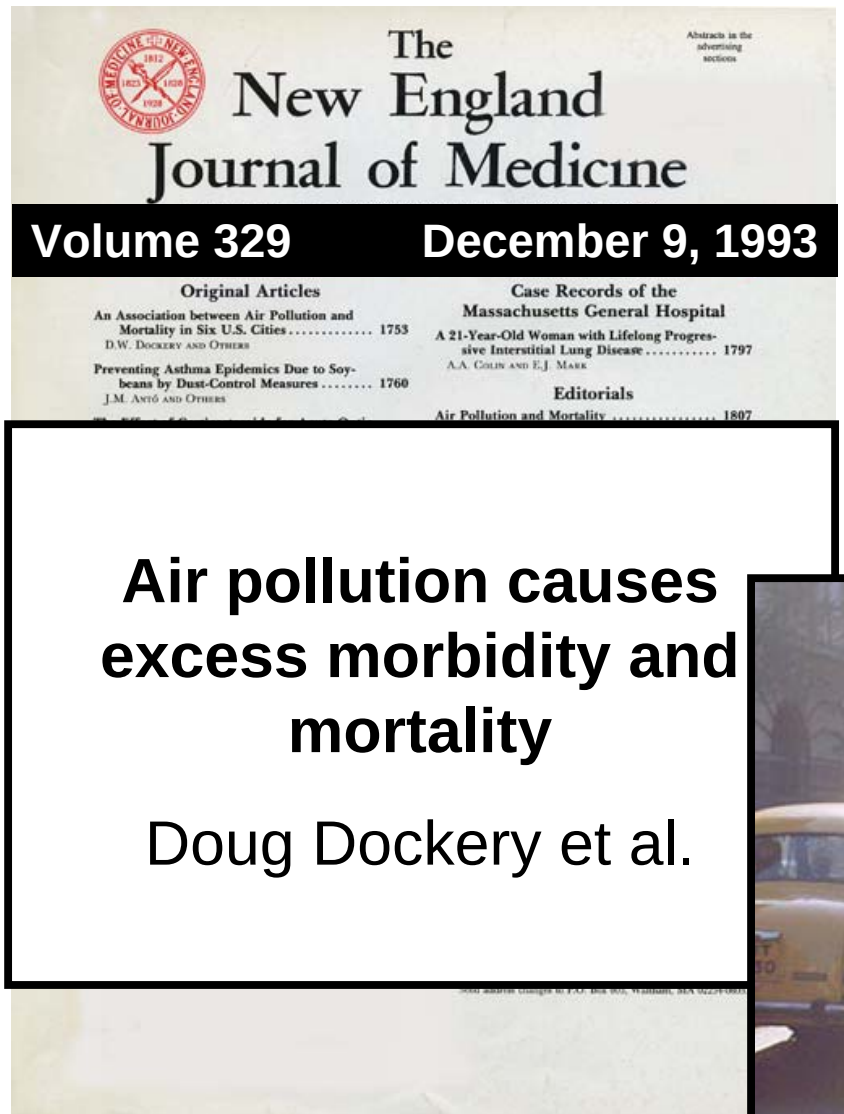
# Prioritize Diseases and Populations

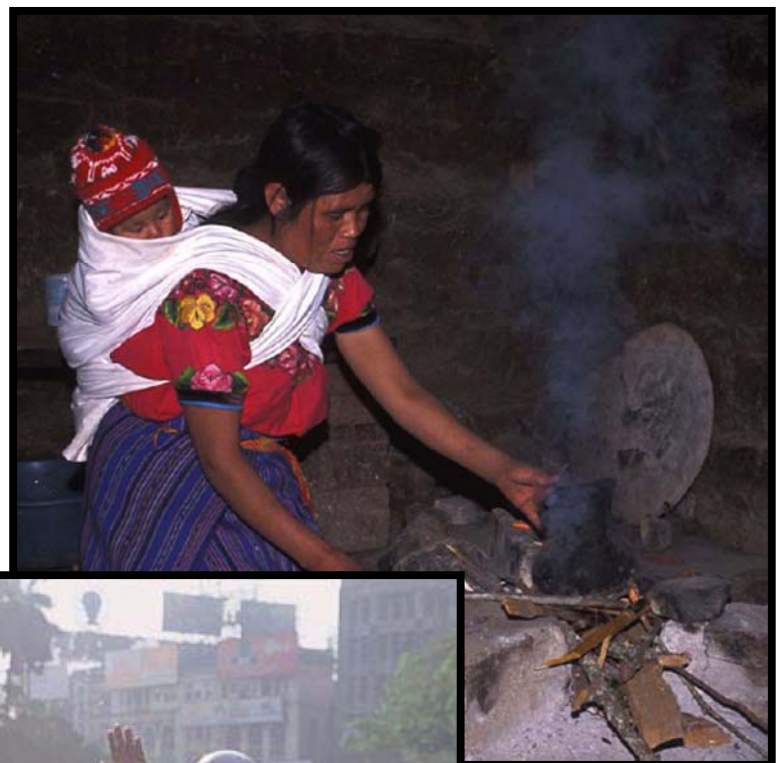
- **International patterns of disease (rates, geographical distribution)**
- **Familial and twin studies (genetic vs. environmental contribution to disease phenotype)**
- **Populations exposed to high concentrations of common toxins**

# Global Environmental Health




# Global Environmental Health



**Air pollution causes excess morbidity and mortality**

Doug Dockery et al.

# Priorities for Program Development

- Impact on Human Health and Disease
  - Programmatic research focusing on complex human diseases
  - Enhance role of physician scientist
- Environmental Genomics
  - Epigenetics
  - Comparative biology/genomics
  - Training in environmental genomics
- Exposure Biology Initiative
- Global Environmental Health